Stavudine (d4T, Zerit)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Oral Solution: 1 mg/mL

Capsules: 15 mg, 20 mg, 30 mg, and 40 mg

Generic: d4T capsules and solution have been approved by the Food and Drug Administration (FDA) for manufacture and distribution in the United States.

Dosing Recommendations

Neonate/infant dose (birth to 13 days):
0.5 mg/kg twice daily.

Pediatric dose (14 days and body weight <30 kg):
1 mg/kg twice daily.

Adolescent (body weight ≥30 kg)/adult dose:
30 to <60 kg: 30 mg twice daily.
≥60 kg: 40 mg twice daily*.

* The World Health Organization (WHO) recommends 30 mg twice daily regardless of body weight in adults (see Pediatric Use).

Selected Adverse Events

- Mitochondrial toxicity
- Peripheral neuropathy
- Lipoatrophy
- Pancreatitis
- Lactic acidosis/severe hepatomegaly with hepatic steatosis (higher incidence than with other nucleoside reverse transcriptase inhibitors [NRTIs])
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- Rapidly progressive ascending neuromuscular weakness (rare)

Special Instructions

- d4T can be given without regard to food.
- Shake d4T oral solution well before use. Keep refrigerated; the solution will remain stable for 30 days.

Metabolism

- Renal excretion 50%. Decrease dose in renal dysfunction.

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)***:***

- *Renal elimination:* Drugs that decrease renal function could decrease stavudine clearance.
- *Other NRTIs:* Stavudine should not be administered in combination with zidovudine because of virologic antagonism.
- *Overlapping toxicities:* The combination of stavudine and didanosine is not recommended for initial therapy because of overlapping toxicities. Toxicities are more often reported in adults and include se-

rious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women.

- *Ribavirin and interferon:* Hepatic decompensation (sometimes fatal) has occurred in HIV/hepatitis C virus (HCV) coinfected patients receiving combination antiretroviral therapy (cART), interferon, and ribavirin.

Major Toxicities:

- *More common:* Headache, gastrointestinal (GI) disturbances, skin rashes, hyperlipidemia, and fat maldistribution.
- *Less common (more severe):* Peripheral neuropathy and pancreatitis. Lactic acidosis and severe hepatomegaly with hepatic steatosis, including fatal cases, have been reported. The combination of stavudine with didanosine may result in enhanced toxicity (increased risk of fatal and nonfatal cases of lactic acidosis, pancreatitis, and hepatotoxicity), particularly in adults, including pregnant women. This combination should not be used for initial therapy.
- *Rare:* Increased liver enzymes, rapidly progressive ascending neuromuscular weakness.

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html), and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/d4T.html).

Pediatric Use: Although stavudine is FDA approved for use in children, its use is limited because it carries a higher risk of side effects associated with mitochondrial toxicity and a higher incidence of lipoatrophy than other NRTIs.

Data from multiple pediatric studies of stavudine alone or in combination with other antiretrovirals (ARVs) demonstrate that stavudine appears safe and is associated with clinical and virologic response[1-7]. In resource-limited countries, stavudine is frequently a component of initial cART therapy with lamivudine and nevirapine in children, often as a component of fixed-dose combinations not available in the United States. In this setting, reported outcomes from observational studies are good; data show substantial increases in the CD4 count and complete viral suppression in 50%–80% of treatment-naive children[8-11]. In such a setting, where pediatric patients are already predisposed to anemia because of malnutrition, parasitic infestations, or sickle cell anemia, stavudine carries a lower risk of hematologic toxicity than zidovudine, especially in those patients requiring cotrimoxazole prophylaxis[12].

Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving cART[13-14]. In a large pediatric natural history study (PACTG 219C), stavudine-containing regimens had a modest but significantly higher rate of clinical and laboratory toxicities than those containing zidovudine, with pancreatitis, peripheral neuropathy, and lipodystrophy/lipoatrophy (fat maldistribution) associated more often with stavudine use[14]. Peripheral neuropathy is an important toxicity associated with stavudine but appears to be less common in children than in adults[2, 15]. In PACTG 219C, peripheral neuropathy was recognized in 0.9% of children[14]. Lipodystrophy, and specifically lipoatrophy (loss of subcutaneous fat), are toxicities associated with the use of NRTIs, particularly stavudine, in adults and children[16-19]. Lipodystrophy developed in 28% of 39 children receiving stavudine, lamivudine, and nelfinavir after a median of 49 months of therapy, with 9 children demonstrating lipoatrophy[20]. Among 90 children receiving stavudine, lamivudine, and either nevirapine or efavirenz, 65% developed lipodystrophy at 33 months[21].

Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with the use of nucleoside analogues, including stavudine, alone or in combination[22-24]. The combination of stavudine and didanosine in pregnant women has been associated with fatal lactic acidosis and should be used during pregnancy only if no other alternatives are available[25]. (For additional information on lactic acidosis see Table 17g Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations.)

Many of the above-mentioned adverse events are believed to be due to mitochondrial toxicity resulting from inhibition of mitochondrial DNA polymerase gamma, with depletion of mitochondrial DNA in fat, muscle, peripheral blood mononuclear cells (PBMCs), and other tissues[22, 26-28]. In a recent analysis involving a large cohort of pediatric patients (Pediatric AIDS Clinical Trials Group protocols 219 and 219 C), possible mitochondrial dysfunction was associated with NRTI use, especially in those children receiving stavudine and/or lamivudine[29].

WHO recommends that stavudine be phased out of use because of serious, irreversible side effects and that a maximum stavudine dose of 30 mg be used instead of the FDA-recommended 40 mg in adults weighing 60 kg or more. Several studies have compared the efficacy and toxicity of the two doses: HIV suppression was found to be similar in adult patients treated in South Africa with either the 30-mg or 40-mg dose[30]; the incidence of peripheral neuropathy in adults treated in South Africa was significantly lower in the 30-mg group than in the 40-mg group, but the overall incidence was considered to be unacceptably high[31]. To reduce the risk of or to manage toxicity, some Panel members support switching to another agent if available rather than lowering the maximum dose. This recommendation is based on the availability of alternative ARV agents in the United States and on concerns for underdosing some patients with stavudine. However, other Panel members prefer using the 30-mg maximum dose of stavudine when there are limited alternatives.

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